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A Synthesis of (±)-Hymenin

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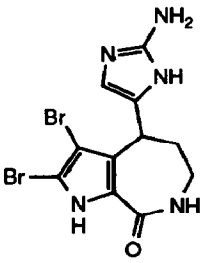
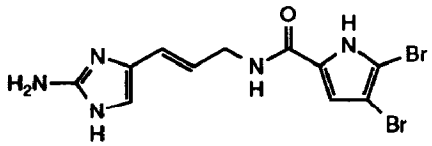
Abstract: (±)-Hymenin (**1**) has been synthesized by a highly efficient route involving the generation of an azafulvene intermediate and its coupling with 2-aminoimidazole.

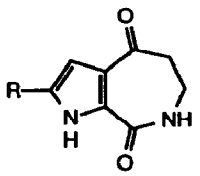
Certain marine sponges produce a structurally interesting and pharmacologically active class of $C_{11}N_5$ metabolites that are comprised of two major heterocyclic units, namely, derivatives of pyrrole and 2-aminoimidazole.[1] Hymenin (**1**) is representative of bicyclic members within this family of alkaloids and was isolated from an Okinawan sponge, *Hymeniacidon* sp.[2] Biological evaluation of this metabolite demonstrated that **1** possesses potent α-adrenoceptor blocking properties.[2,3] The structure of **1**[2,4] was elucidated from spectral studies primarily in comparison with the biogenetically and structurally related alkaloid, oroidin (**2**).[5,6] An interesting structural feature of **1** is the fused bicyclic azepine skeleton, which is unique among marine natural products. In this communication we describe an efficient synthesis of (±)-**1** using a route that involves an acid-promoted generation of an azafulvene intermediate **A** (R=Br) and its coupling with 2-aminoimidazole (AI).[7]



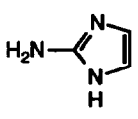
1



2



3 R = H, Br

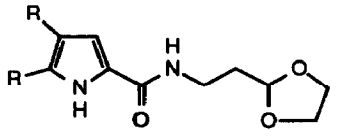


AI

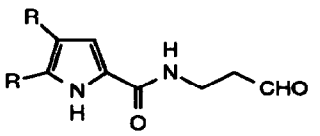
Related to this family of alkaloids exist metabolites that lack the AI appendage such as bicyclic ketones **3**. These ketones were isolated from the New Caledonian sponge *Pseudaxinyssa* sp.[8,9] and may hypothetically serve as biogenetic and synthetic precursors to **1**. In particular, we felt that olefin **6**, which is a reduced synthetic equivalent of ketone **3**, would be a suitable intermediate for the delayed introduction of the

AI moiety. Protonation of **6** would lead to the electrophilic azafulvene intermediate **A** and, therefore, would be expected undergo coupling with AI. This type of reaction is reminiscent of the hydroxyalkylation of 2-aminoimidazoles with aldehydes,[10] a process that was used in the synthesis of the tricyclic marine pigments zoanthoxanthins.[11]

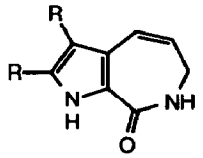
Starting with 2-trichloroacetylpyrrole[12] and 2-(2-aminoethyl)-1,3-dioxolane,[13] acylation (CH_3CN, 23 °C, 16 h) of the amino group proceeded smoothly to afford debromopyrrole **4a**[14] in 85% yield. Although the pyrrole group in hymenin (**1**) is dibrominated, the debromo derivative was initially prepared because we wanted to address the issue of when the bromine atoms could be incorporated into the pyrrole during the synthesis. In principle, the incorporation could occur either prior to or after the construction of the bicyclic core. Hydrolysis of acetal **4a** (*p*TsOH, 1:1 acetone:water, reflux) gave aldehyde **5a**, which underwent intramolecular cyclization to bicyclic olefin **6a**[15] in trifluoroacetic acid (24 h, 23 °C). Only small amounts (10%), however, of the desired olefin could be obtained. The major product of the reaction is dimer **7**.[16] ^1H and ^{13}C NMR data for **7** in comparison to those of the monomer **6a** clearly indicate that dimerization proceeded at the more nucleophilic α-carbon of intermediate **A**. Further attempts to increase the yield of **6a** by heating **5a** in benzene, toluene, or xylene under neutral or acidic conditions were unsuccessful.



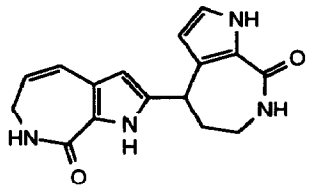
4a R = H
4b R = Br



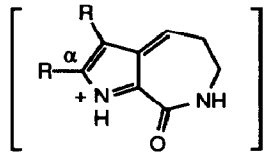
5a R = H
5b R = Br



6a R = H
6b R = Br



7



A R = H or Br

All attempts to couple **6a** with AI under acidic conditions failed. Only dimerization to **7** was observed. These results necessitated the incorporation of bromine into the pyrrole prior to cyclization.

Starting from 4,5-dibromo-2-trichloroacetylpyrrole,[17] acetal **4b** and aldehyde **5b** were analogously prepared in good yields. Treatment of **5b** in trifluoroacetic acid gave only small amounts of **6b** along with predominantly unreacted starting material. In order to facilitate the cyclization a stronger acid was utilized. When aldehyde **5b** was exposed to methanesulfonic acid (23 °C, 3 days) an 80% yield of bicyclic olefin **6b** was obtained without the formation of dimeric products.[18] Activation of olefin **6b** to azafulvene intermediate **A** (R=Br) in the presence of AI (CH_3SO_3H, 23 °C, 3 days) afforded a 70% yield of (±)-hymenin (**1**)[19] as a colorless solid. Alternatively, (±)-hymenin (**1**) can be prepared directly from aldehyde **4b** and AI without isolation of bicyclic olefin **5b** by stirring both reactants in methanesulfonic acid for 5 days at 23 °C. ^1H and

^{13}C NMR, UV, IR and MS data of synthetic (±)-**1** were in complete agreement with values reported for the natural material.[2] The use of strongly acidic media serves two important purposes. The proton serves as a natural protecting group for nitrogen on AI and it is also used to generate the azafulvene electrophile from olefin **6**. As a result, only newly formed carbon-carbon bond products that are non-acid labile predominate under these conditions.

Since a number of marine natural products are brominated, including the vast majority of oroidin related alkaloids, it follows that halogenation (oxidation) may play a key role in the biosynthesis of these metabolites.[20] Indirect experimental support for these hypotheses has been provided by the Büchi laboratory. The bromine promoted oxidation of dihydrooroidin to dibromophakellin,[21a] hymenin (**1**)[21b] and oroidin (**2**)[21b] suggests that oxidation of the aminoimidazole unit followed by intramolecular cyclization/elimination events may, in fact, closely parallel the biosynthetic pathway. The actual biosynthesis of **1** has not been determined and one wonders if non-oxidative processes could be occurring. Our studies indicate that such processes are involved conceivably in both the cyclization and the AI coupling steps wherein the final two carbon-carbon bonds of **1** are formed.

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† Beckman Young Investigator, 1992-1994.

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14. All compounds gave satisfactory spectral and analytical analysis.
15. **6a**, colorless powder, mp 156-160 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (t, J=5.6 Hz, 2H), 5.87 (dt, J=10.0, 6.4 Hz, 1H), 6.24 (t, J=2.6 Hz, 1H), 6.38 (bs, 1H), 6.77 (d, J=10.0 Hz, 1H), 6.99 (t, J=2.7 Hz, 1H), 10.46 (bs, 1H); ^{13}C NMR (75.2 MHz, CD_3OD) δ 40.0 (t), 110.0 (d), 123.8 (d), 124.1 (d), 125.8 (s), 127.7 (s), 129.3 (s), 166.7 (s); MS (DCI, CH_4) m/z 148 (M^+, 55), 119 (40), 105 (12), 92 (25); UV (MeOH) λmax 223 nm (ε 16 320), 276 (5 200).
16. **7**, colorless powder, mp 199-202 °C (dec); ^{1}H NMR (400 MHz, CD_3OD) δ 2.16 (m, 2H), 3.22 (m, 2H), 3.44 (d, J=6.6 Hz, 2H), 4.33 (t, J=6.1 Hz, 1H), 5.73 (dt, J=9.9, 6.6 Hz, 1H), 5.73 (s,1H), 5.88 (d, J=2.5 Hz, 1H), 6.56 (d, J=9.9 Hz, 1H), 6.83 (d, J=2.5 Hz, 1H); ^{13}C NMR (75.2 MHz, CD_3OD) δ 35.3 (t), 38.9 (d), 40.0 (t), 40.3 (t), 108.9 (d), 112.5 (d), 123.0 (s), 123.5 (d), 123.8 (d), 124.5 (s), 127.4 (s), 128.1 (s), 129.3 (d), 143.4 (s), 166.4 (s), 166.8 (s); MS (DCI, NH_3) m/z 297 (M^++1, 72); UV (MeOH) λmax 226 nm (ε 24 310), 271 (15 440).
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18. Olefin **6b** can be also prepared directly from acetal **4b** (CH_3SO_3H, 23 °C) although the reaction time is much longer.
19. (±)-**1**, colorless powder, mp 86-88 °C (dec); ^{1}H NMR (300 MHz, CD_3OD) δ 1.92 (m, 1H), 2.25 (m, 1H), 3.06 (dd, J=14.0, 7.3 Hz, 1H), 3.16 (dd, J=14.0, 9.8 Hz, 1H), 4.12 (t, J=3.5 Hz, 1H), 5.88 (s, 1H); ^{13}C NMR (75.2 MHz, CD_3OD) δ 32.7 (t), 37.9 (t), 38.4 (d), 102.8 (s), 107.7 (s), 113.0 (d), 125.3 (s), 128.5 (s), 136.8 (s), 150.6 (s), 164.2 (s); IR (Nujol) cm^{-1} 3360, 3270, 3150, 1680, 1625, 1566, 1481, 1425, 1327, 1216, 1095, 949; MS (DCI, CH_4) m/z 390 (M^++3, 50), 388 (M^++1, 35), 312 (22), 112 (100); UV (MeOH) λmax 275 nm (ε 9 560);
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